Specialized tip/stalk-like and phalanx-like endothelial cells from embryonic stem cells.

Journal: Stem Cells Dev

Publication Year: 2013

Authors: Alicia A Blancas, Lian E Wong, Drew E Glaser, Kara E McCloskey

PubMed link: 23249281

Funding Grants: Building Cardiac Tissue from Stem Cells and Natural Matrices

Public Summary:
Endothelial cells (EC) generated in vitro from stem cells are desirable for their potential in a variety of in vitro models and cell-based therapeutic approaches; however, EC can take on a number of functionally and phenotypically distinct specializations. Here, we show the generation of functionally distinct EC subpopulations, including (1) the pro-angiogenic migrating tip-like and proliferative stalk-like EC, and (2) the less migratory cobblestone-shaped phalanx-like EC. Both embryonic stem cell (ESC)-derived EC subpopulations are generated from outgrowths of Flk-1+ vascular progenitor cells with high levels of vascular endothelial growth factor treatment, while the phalanx-like ESC-derived EC (ESC-EC) are subsequently isolated by selecting for cobblestone shape. Compared with the ESC-derived angiogenic endothelial cells (named ESC-AEC) that contain only 14% Flt-1+ and 25% Tie-1+ cells, the selected phalanx-like ESC-EC express higher numbers of cells expressing the phalanx markers Flt-1+ and Tie-1+, 89% and 90%, respectively. The ESC-AEC also contain 35% CXCR4+ tip cells, higher expression levels of stalk marker Notch-1, and lower expression levels of Tie-2 compared with the phalanx-type ESC-EC that do not contain discernible numbers of CXCR4+ tip cells. Perhaps most notably, the ESC-AEC display increased cell migration, proliferation, and 3 times more vessel-like structures after 48 h on Matrigel compared with the phalanx-like ESC-EC. This work analyzes, for the first time, the presence of distinct EC subtypes (tip/stalk, and phalanx) generated in vitro from ESC, and shows that phalanx-like EC can be purified and maintained in culture separate from the tip/stalk-like containing EC.

Scientific Abstract:
Endothelial cells (EC) generated in vitro from stem cells are desirable for their potential in a variety of in vitro models and cell-based therapeutic approaches; however, EC can take on a number of functionally and phenotypically distinct specializations. Here, we show the generation of functionally distinct EC subpopulations, including (1) the pro-angiogenic migrating tip-like and proliferative stalk-like EC, and (2) the less migratory cobblestone-shaped phalanx-like EC. Both embryonic stem cell (ESC)-derived EC subpopulations are generated from outgrowths of Flk-1+ vascular progenitor cells with high levels of vascular endothelial growth factor treatment, while the phalanx-like ESC-derived EC (ESC-EC) are subsequently isolated by selecting for cobblestone shape. Compared with the ESC-derived angiogenic endothelial cells (named ESC-AEC) that contain only 14% Flt-1+ and 25% Tie-1+ cells, the selected phalanx-like ESC-EC express higher numbers of cells expressing the phalanx markers Flt-1+ and Tie-1+, 89% and 90%, respectively. The ESC-AEC also contain 35% CXCR4+ tip cells, higher expression levels of stalk marker Notch-1, and lower expression levels of Tie-2 compared with the phalanx-type ESC-EC that do not contain discernible numbers of CXCR4+ tip cells. Perhaps most notably, the ESC-AEC display increased cell migration, proliferation, and 3 times more vessel-like structures after 48 h on Matrigel compared with the phalanx-like ESC-EC. This work analyzes, for the first time, the presence of distinct EC subtypes (tip/stalk, and phalanx) generated in vitro from ESC, and shows that phalanx-like EC can be purified and maintained in culture separate from the tip/stalk-like containing EC.